REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 28-46 are currently under consideration. Claims 29 and 32 are cancelled and claims 28 and 31 are amended without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

The Examiner is thanked for entering the Information Disclosure Statement filed on February 6, 2007. The Examiner is also thanked for granting the benefit date of September 12, 2000. The Examiner is further thanked for withdrawing the rejections under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 112, first paragraph.

It is submitted that the claims herewith are patentably distinct over the prior art, and these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims presented herein are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply to clarify the scope of protection to which Applicants are entitled.

II. REJECTION UNDER 35 U.S.C. § 112, 1ST PARAGRAPH IS OVERCOME

Claims 28 and 30-34 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Office Action contends that although the scope of claims 28 and 30-34 is smaller than previously claimed, the scope of the amended claims is still much greater than the specification provides.

Although the Applicants do not agree with the Office Action, in the interest of expediting prosecution, claim 28 has been amended to introduce claim 29 into claim 28.

As Applicants have stated previously, the presently claimed invention is also supported by Li et al. (Cancer Gene Therapy, 2003:10:105-111), published after the instant application, that a bacterium of the genus Bifidobacterium other than Bifidobacterium Longum can be used. Li et al uses the instant invention with Bidifocaterium adolescentis, a bacterium of the genus Bifidobacterium other than Bifidobacterium longum. This is clear from that Li et al. cites Yazawa (Cancer Gene Ther. 2000; 7:269-274), and thus, it is clear that Li et al has used the instant invention according to the knowledge of Yazawa.

Furthermore, Applicants also provide the deposit information of other Bifidobacterium strains (see, e.g., ¶ 209 of the specification as published), therefore providing additional examples of Bifidobacterium in addition to Bifidobacterium Longum.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112 first paragraph is respectfully requested.

III. REJECTIONS UNDER 35 U.S.C. § 103(a) ARE OVERCOME

Claims 28-46 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yazawa (Proceedings of the American Association for Cancer Research Annual Meeting 40: 88, 1999; hereinafter "Yazawa") in view of Brown et al. (U.S. Patent No. 6,416,754B1; hereinafter "Brown"). Applicants respectfully traverse this rejection.

The specification of the instant application recites: "However, these bacteria have pathogenicity in humans and are thus not always safe gene delivery vectors in gene therapy of solid tumors. Actually, some reports have demonstrated febrile adverse reactions as side effects after injection with Clostridium butyricum spores or oral intake of Salmonella typhi (Eur. J. Cancer. 3: 37-41 (1967), J. Clin. Invest. 90: 412-420 (1992), Infect. Immun. 60: 536-541 (1992))."and it is clear that it has been reported in 1992 that Clostridium is not always safe as a gene delivery vector in gene therapy of solid tumors, which is before the filing date of Brown (March 3, 1994).

Brown relates to a method of gene delivery involving sporulation, which recites "Antitumor activity is optimally produced by spores rather than the vegetative form (Mose and Mose, supra), and C. Actobutylicum produces spores under the conditions present in the targeted tumor. (Brown et al.; [0147])"(column 5, line 19029), and it has been clarified that antitumor activity is "optimally produced by spores rather than the vegetative form".

This sporulation method is also described in Examples 1, 2, and 4 of Brown. Brown's recitation that the spore form is the optimal embodiment teaches away from the vegetative form of bacteria used in the instant invention. Further, even it is a similar anaerobic bacterium, there is a possibility that spores transfers at random to normal tissues, and spore differs significantly from vegetative form.

In Example 2, Brown uses spores of Clostridium after killing vegetative forms by heat shocking at 80°C for 20 min before administration. On the other hand, the instant invention relates to a bacterium belonging to the genus Bifidobacterium. As the bacterium belonging to the genus Bifidobacterium is not a spore-forming bacterium, the instant invention uses naturally a vegetative form.

Compared to a vegetative form, spores have a higher resistance to physical and chemical treatments including heating or germicide, and it is relatively easy to administrate in the actual treatment, manufacturing pharmaceutical compositions, and to store, and there is no need to be sensitive.

On the contrary, vegetative form has a very low resistance to physical and chemical treatments including heating or germicides, and as a bacterium belonging to the genus Bifidobacterium is absolutely anaerobic, it is very difficult to administrate in the actual treatment, manufacturing pharmaceutical compositions, and to store, which requires lot of attention.

Therefore, there is no possibility for a motivation to combine the invention of Brown using spores of Clostridium, and the invention of Yazawa using vegetative form of a bacterium belonging to the genus Bifidobacterium. In case there is one, it is merely to consider using vegetative form of the bacterium belonging to the genus Bifidobacterium which is safe, instead of using spores of Clostridium having a problem of safety.

Regarding the above, there is the following description in the instant specification (see, e.g., ¶12, 13 and 17 of the specification as published):

> "In recent years, however, a system for the convenient and reproducible genetic transformation of stains of the genus Bifidobacterium was developed (Microbiology, 142: 109-114 (1996); Biosci. Biotechnol. Biocem. 61: 1211-1212 (1997))."
>
> "However, the development of regulatory sequences including a promoter for highly expressing an introduced gene was still not satisfactory."

> "Further, the present inventors examined a system of genetically transforming the bacteria belonging to the genus Bifidobacterium, and as a result, they found that an introduced gene can be efficiently expressed by using expression vector containing a promoter and a terminator involved in expressing a gene coding for a histone-like DNA-binding protein inherently highly expressed in the bacteria belonging to the genus Bifidobacterium, particularly in Bifidobacterium longum."

And in Example 3, a method for constructing plasmid pBLHU15 having a promoter and terminator of HU gene of Bifidobacterium longum, is disclosed in detail.

The instant invention is characterized by using a vector integrated with a HU gene promoter and terminator, and to express effectively the introduced gene.

To clarify this feature of the instant invention, claim 28 now limits the promoter and terminator to "a promoter and terminator involved in expressing a gene coding for a histone-like DNA binding protein belonging to the genus Bifidobacterium".

On the other hand, the cloning vector of Brown, is characterized by that a promoter of Fd gene has been introduced, as it is described in Example 3. There is no disclosure of a cloning vector in Yazawa.

Thus, there is no teaching neither in Brown or Yazawa, of a bacterium belonging to the genus Bifidobacterium transformed by a cloning vector having a HU gene promoter and terminator that can express effectively the introduced gene.

Therefore, even by combining Brown and Yazawa, the instant invention cannot be achieved. Accordingly, reconsideration and withdrawal of the 35 U.S.C. § 103 rejections are respectfully requested.

IV. REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, ARE OVERCOME

Claim 32 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claim 32 has been cancelled, thereby rendering the rejection moot.

Reconsideration and withdrawal of the 35 U.S.C. § 112, second paragraph, rejection is respectfully requested.

V. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ARE OVERCOME

Claim 32 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Claim 32 has been cancelled, thereby rendering the rejection moot.

Reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph, rejection is respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, an interview with the Examiner and SPE are respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,

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